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Trimeric Cyclamers: Solution Aggregation and High *Z'* Crystals Based on Guest Structure and Basicity

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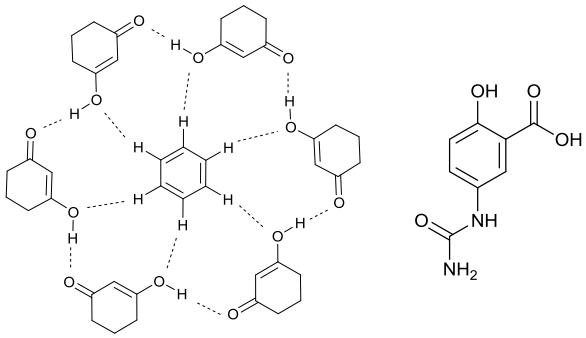
Stuart R. Kennedy, Adeline Miquelot, Juan A. Aguilar and Jonathan W. Steed*

Ureidosalicylic acid forms remarkable trimeric cyclamer-like crystal structures with either three or six independent molecules in the asymmetric unit as a result of the excess of hydrogen bond donors and guest inclusion within the centre of the cyclamer. The structures persist in soluition in hydrogen bond acceptor solvents suggesting a role in solution pre-association in forming high *Z'* structures.

In 1986 Margaret Etter and co-workers reported the first of a series of cyclic structures based on hydrogen-bonded cyclohexane dione and its derivatives.[1, 2] The symmetrical planar structure of these aggregates results in a central cavity suitable for inclusion of a guest such as a solvent molecule. At Etter's suggestion Braga and coworkers went on to host the bis(benzene)chromium cation in partial cyclamer.[3] The most iconic member of the series, the benzene cycla-6-mer, invited suggestion that the assembly is templated or at least assisted by solvent-cyclamer interaction such as CH···O hydrogen bonding (Scheme 1). In the case of related cyclic tin complexes there is evidence that the structure persists in solution,[4] although the hydrogen bonding in the benzene case is likely to be too weak to overcome the entropic penalty of a seven-component assembly for any significant lifetime.

As part of work directed towards compounds possessing orthogonal self-assembling functional groups we prepared the mesalazine derivative 5-ureidosalicylic acid (**1**). We have previously shown that *N*-alkyl derivatives of both 4- and 5-ureidosalicylic acid dimerise by homofunctional recognition to give pairs of molecules linked by the well-known $R_2^2(8)$ carboxylic acid dimer synthon. These dimers in turn self-assemble *via* a double urea α-tape motif, resulting in the formation of supramolecular gel phase materials.[5] In contrast, we now report, surprisingly, that **1** does not exhibit orthogonal homofunctional assembly and instead gives cyclic hydrogen bonded cyclamer-like structures based on a urea-carboxylic acid heterosynthon[6] in the presence of hydrogen bond acceptor guests.



Benzene cyclamer 5-ureidosalicylic adic, **1**

Scheme 1. Structures of Etter's benzene cyclamer[2] and 5-uriedosalicylic acid. The cyclamer structure was subsequently adopted as a logo for *CrystEngComm*

Results and Discussion

Compound **1** was prepared in 57% yield from mesalazine by reaction with sodium cyanate (see supplementary information). Crystals of unsolvated **1** can be obtained from either methanol or ethanol and the compound was characterised by single crystal X-ray crystallography. While the determination is of low precision as a result of very small crystal size and consequent weak diffraction the gross structural details are unambiguous. The urea group adopts an unusual *syn* conformation of the secondary NH group with respect to the carbonyl group. This allows the formation of two distinct 8-membered hydrogen bonded rings, one a urea-urea homosynthon and one a urea-carboxylic acid heterosynthon, Fig. 1. The primary NH_2 group also exhibits a long bifurcated interaction to the phenol OH group O(2) via NH atom H(1A). However, interestingly, the other NH donor H(1B) does not form any significant interactions. This unusual situation exemplifies the fact that the molecule possesses an excess of hydrogen bond donors compared to hydrogen bond acceptors (5 NH or OH groups *vs.* 4 oxygen atom acceptors)

[a] *Department of Chemistry, Durham University, University Science Laboratories, South Road, Durham, DH1 3LE. E-mail: jon.steed@durham.ac.uk; Fax: +44(0)191 384 4737; Tel: +44 (0)191 334 2085*

Electronic Supplementary Information (ESI) available: synthesis and characterisation of **1** and details of single crystal structure determination in CIF format; CCDC 1495375-1495381. See DOI: 10.1039/c000000x/. The underlying research data for this paper is available in accordance with EPSRC open data policy from DOI: 10.15128/r102870v84p.

and hence the presence of this "extra" hydrogen bond donor suggests that the compound might be expected to interact with hydrogen bond acceptor solvents and co-formers.

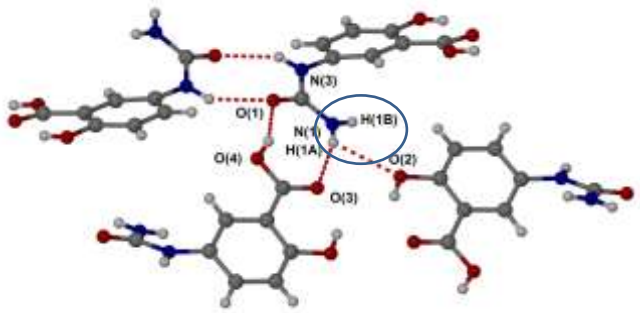


Figure 1. X-ray crystal structure of unsolvated compound **1** showing the urea-urea and urea-carboxylic acid synthons. The NH hydrogen atom H(1B) does not form any significant hydrogen bonds and is "surplus".

Crystallization of **1** from tetrahydrofuran (THF) results in a THF solvate **1**·THF with a remarkable cyclamer-like trimeric structure based on 8-membered hydrogen bonded ring synthons between the carboxylic acid and urea functionalities, Fig. 2. This relatively common synthon is exemplified in a recent report of the polymorphism of carglumic acid which can crystallize with either acid···acid or acid···amide hydrogen bonding.[7] The synthon is also found in a co-crystal of 5-nitrosalicyclic acid and phenylurea.[8] However, the hydrogelator 5-(((3-nitrophenyl)carbamoyl)amino)isophthalic acid which possesses a similar meta aryl arrangement to **1** crystallises with urea···urea, urea···nitro and carboxylic acid dimer motifs.[9] In the present case, the cyclic trimer in **1**·THF is held together by very short OH···O interactions with O···O distances in the range 2.51 – 2.53 Å and longer NH···O interactions 2.93 – 3.02 Å. The phenolic OH groups are involved in intramolecular OH···O interactions and hence two *syn* urea NH groups are "surplus" at the periphery of the trimeric assembly without hydrogen bonding partners. These NH groups form bifurcated acceptor interactions with the oxygen atom of the included THF guests. It is noteworthy that the urea group adopts a very different *anti* conformation with respect to the internal NH and carbonyl groups in comparison to the *syn* unsolvated structure. This arrangement exposes the two NH groups on the trimer periphery. While the trimer possesses approximate threefold symmetry, the entire assembly is crystallographically unique. This situation arises because two THF guest molecules per trimer (based on O14 and O15) nest above and below the void space at the centre of the ring of adjacent trimers (Fig. 2b), while the third THF molecule is situated in between trimer-included solvent molecules and gives rise to an infinite THF-filled channel. The fact that the molecular structure favours a threefold assembly but there are only two void positions in the middle of the self-assembled trimer for solvent inclusion is a fundamental mismatch or "frustration"[10] that means that the *whole structure must be crystallographically unique*, *i.e.* there must be three formula units in the asymmetric unit, $Z' = 3$.[11, 12] The topic of crystal structures with $Z' > 1$ has been of considerable recent interest and has been comprehensively reviewed.[13] Nangia has also reported crystallographically unique threefold assemblies.[14]

TGA analysis of the THF cyclamer reveals relatively facile solvent loss as a gradual process between 50 – 110°C. However the total mass loss is far less than implied by the formula implying that desolvation occurs on storage or during instrument equilibration and hence transformation from the solvated to desolvated form is facile even at room temperature.

The self-assembly behaviour of solvates of **1** represents an interesting opportunity to test this structural frustration concept, particularly since the hydrogen bond acceptor THF not only occupies void space in the middle of the cyclamer but also interacts with the urea NH groups at the periphery of an adjacent assembly. Accordingly we undertook an extensive solvate screen for **1** and obtained and crystallographically characterised a further 5 solvates of considerable complexity.

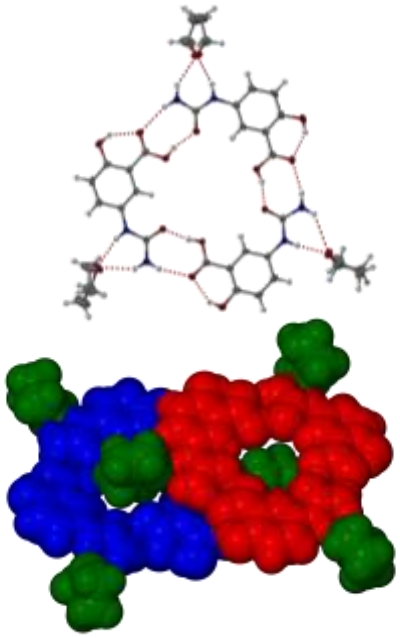


Figure 2. (a) Trimeric assembly in **1**·THF (b) two symmetry-related trimers in **1**·THF (red and blue) showing the inclusion of the THF guest species (green).

Crystallization of **1** from acetonitrile and acetone (like THF, hydrogen bond acceptor solvents with little hydrogen bond donor ability) also resulted in 1:1 solvates based on the cyclic trimer motif. However, in both cases the crystallographic asymmetric unit comprises *two* symmetry independent trimers, and six independent solvent molecules, $Z' = 6$, $Z'' = 12$ (where Z'' is the total number of symmetry independent molecules in the asymmetric unit[15]). In the case of **1**·MeCN the acetonitrile included in the centre of the cyclamer cavity penetrates rather more deeply than THF and hence only a single solvent molecule is included. The opposite face of each cyclamer stacks with an adjacent trimer. The included acetonitrile also hydrogen bonds with the urea group of another adjacent cyclamer and hence the interactions

between cyclamers simultaneously incorporate π-stacking on one face and hydrogen bonding to inclined, included acetonitrile on the other (Fig. 3). This feature gives rise to two independent cyclamers of slightly differing conformation, both more planar than in **1**·THF. The hydrogen bonding interactions to the six independent acetonitrile molecules are all loosely of the $R_2^1(6)$ type however the NH···N distances vary widely from 2.98 – 3.54 Å as a result of the need to simultaneously accommodate the cyclamer inclusion of some molecules, optimise π-stacking interactions and fill space efficiently.

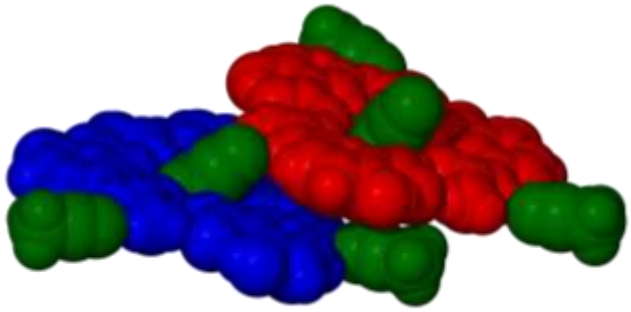


Figure 3. The crystallographic asymmetric unit in **1**·MeCN showing the urea hydrogen bonding to a cyclamer-included molecule of acetonitrile.

The acetone solvate also possesses two independent cyclamer motifs (*Z*′ = 6) and in a similar way to the acetonitrile and THF solvates the complex packing arrangement is determined by the simultaneous inclusion of the hydrogen bond acceptor guest within the cyclamer cavity and hydrogen bonding from the peripheral urea NH groups to the acetone carbonyl oxygen atom. In this case the cyclamer cavity is occupied by the bulkier acetone solvent molecule on both faces. On one face an acetone methyl group points into the cavity while on the opposite face the acetone guest is approximately coplanar with the cyclic trimeric host structure. Each independent acetone guest hydrogen bonds to the urea groups of adjacent cyclamers with NH···O distances again varying widely from 2.87 – 3.30 Å.

In all three cyclamer solvates the highly complex asymmetric unit arises from the simultaneous need to fill the cyclamer cavity and optimise hydrogen bonding from the 'excess' urea NH groups to the hydrogen bond acceptor solvent guest. Such assemblies could also form in H-bond acceptor solution and hence represent the crystal "growth unit" and contribute to the observed high *Z*′ structure.[13] The DOSY NMR spectrum of **1** in acetone-d_6 shows that the compound has a remarkably low diffusion coefficient of 15.64 ± 0.06 m^2s^{-1} in comparison to a reference compound *o*-xylene (32.0 ± 0.2 m^2s^{-1}). Using the method of Morris and coworkers[16] the DOSY spectrum yielded an apparent molecular mass of 388.6 g mol^{-1}, in comparison to the mass of a monomer of 196 g mol^{-1}. This value represents an average over an equilibrating mixture of monomeric and oligomeric species and implies that the trimer is likely to be a significant species in this medium.

Assemblies based on **1** with weaker hydrogen bond acceptors might be expected to adopt a more symmetrical structure or an entirely different packing mode, particularly if trimeric association were disfavoured in solution. This is indeed the case with the nitrobenzene solvate. Rather poorly diffracting crystals of a 1:1 solvate were eventually obtained from nitrobenzene solution and their structure analysed using I19 at the Diamond synchrotron. Nitrobenzene is sterically bulky and the nitro group is a poor hydrogen bond acceptor.[17, 18] As a result the cyclic trimer motif is not produced at all. Instead the resulting crystals prove to be of tetragonal, non-stoichiometric channel solvate based on a very strange cyclic tetrameric motif. The urea carbonyl acceptor forms both a high distorted urea α-tape motif based on $R_2^1(6)$ hydrogen bonded rings and also a urea-carboxylic acid $R_2^2(8)$ motif as observed in the THF, acetonitrile and acetone solvates. Hence in this structure the urea carbonyl group fulfils the hydrogen bond acceptor role for the "surplus" urea NH groups played by the THF, MeCN or acetone solvent in the cyclamer structures. As a result the urea carbonyl group accepts a total of three strong hydrogen bonding interactions, Fig 4a. The nitromethane solvent is highly disordered in the crystal channel and was treated with the Platon SQUEEZE procedure.[19] This yielded a channel of 730 $Å^3$ per 2312 $Å^3$ unit cell (32%). The Platon electron density of 358 e^- per cell corresponds to 5.6 molecules of nitrobenzene, hence a host : solvent stoichiometry of approximately 1 : 0.7. This formulation implies a surprisingly densely packed channel. Interestingly, because there are no significant host-guest interactions there is only a single crystallographically unique host molecule.

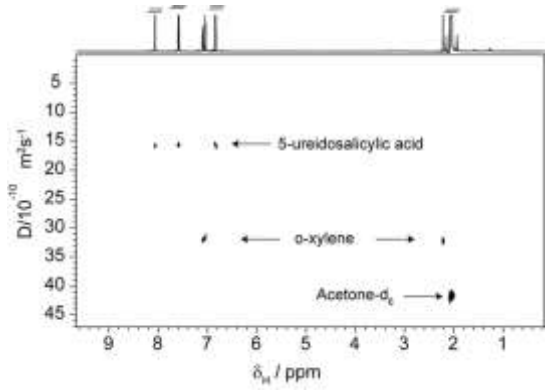


Figure 4. DOSY NMR spectrum of **1** in acetone-d_6 in the presence of *o*-xylene internal reference.

Crystals suitable for single crystal analysis we also obtained from a solution of **1** in 4-picoline (4-methylpyridine), a sterically bulky hydrogen bond acceptor. By analogy with the THF structure a trimeric cyclamer might be expected, however the high basicity of the picoline results in an alternative structure. The resulting 1:2 solvate is based on strong hydrogen bonding to the picoline nitrogen atoms from both the carboxylic acid proton and the 'excess' urea NH proton, hence giving rise to a host:guest 1:2 stoichiometry. The remaining two urea NH protons then interact with the urea carbonyl to give a classic urea α-tape motif (see supplementary information, Fig. S3). There are two independent α-tape strands in the structure, *Z*′ = 2, *Z*′′ = 6

which accommodate edge-to-face stacking interactions between the urea tape and the pyridyl ring.

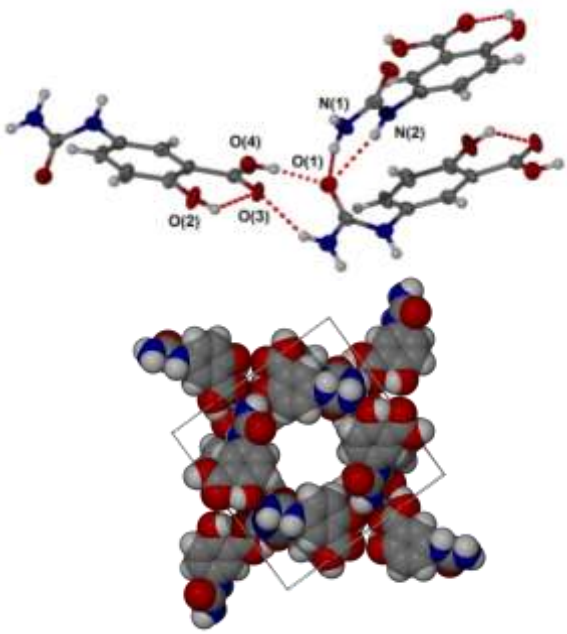


Figure 4. (a) urea environment in the nitrobenzene inclusion compound of **1**. Hydrogen bond distances (Å): N1···O1 3.056(5), N2···O1 2.935(5) and O4···O1 2.610(4). (b) Crystal packing in the nitrobenzene solvate viewed down the tetragonal channel axis.

Finally we were also able to obtain a monohydrate form of **1** by crystallization from water and the X-ray crystal structure is shown in Fig. 6. As in the 4-picoline case the water acts as a hydrogen bond acceptor for the carboxylic acid functional group, hence disrupting the acid-urea heterosynthon and resulting in the formation of the classic urea α-tape arrangement. However, the water is smaller in size than 4-picoline and is also able to accept two hydrogen bonds as well as act as a double hydrogen bond donor. As a result the water molecule is hydrogen bond saturated and forms an infinite 1D chain. Each water molecule accepts two interactions from the carboxylic acid and an adjacent water molecule and also donates two interactions, one to the urea carbonyl (which hence accepts a total of three hydrogen bonds) and one to the next water molecule in the chain (see supplementary information, Fig. S4).

Conclusions

The simple molecule 5-ureidosalycylic acid (**1**) exhibits complex self-assembly behaviour as a result of its non-linear geometry and excess of strong hydrogen bond donor groups over hydrogen bond acceptors. In the solid state the pure material exhibits an unusual "surplus" NH donor and as a result the compound exhibits a significant propensity to form solvates/cocrystals. Hydrogen bond acceptor solvents of the correct size to fit into the cyclamer cavity (MeCN, acetone and THF) result in the formation of cyclic trimers reminiscent of Etter's iconic cyclamers. The low symmetry of the trimer structure results in a large number of crystallographicallly independent molecules in the asymmetric unit. Moreover this symmetry can be further lowered in order to optimise cyclamer inclusion and interactions to the 'excess' hydrogen bond donors in an adjacent cyclamer. The fact that each trimer has three excess NH donors but only two voids above and below the cavity to accommodate solvent molecules is a further source of "frustration" leading to low symmetry. In the case of nitromethane, a solvent with poor hydrogen bond acceptor ability, the system forms additional hydrogen bonding interactions to the urea carbonyl group giving rise to an alternate cyclic structure. The very highly effective hydrogen bond acceptors picoline and water compete successfully for the carboxylic acid functionality resulting in the formation of a classic urea α-tape motif. It is thus possible in this system to rationalise the formation of these attractive cyclameric trimers and understand their propensity to form high *Z*' crystals on the basis of purely molecular structural factors and hydrogen bond donor/acceptor ratio.

Acknowledgments

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Notes and references

1. M. C. Etter, D. L. Parker, S. R. Ruberu, T. W. Panunto and D. Britton, *J. Incl. Phenom. Mol. Recogn. Chem.*, 1990, **8**, 395.
2. M. C. Etter, Z. Urbanczyklipkowska, D. A. Jahn and J. S. Frye, *J. Am. Chem. Soc.*, 1986, **108**, 5871.
3. D. Braga, A. L. Costa, F. Grepioni, L. Scaccianoce and E. Tagliavini, *Organometallics*, 1997, **16**, 2070.
4. T. P. Lockhart, *Organometallics*, 1988, **7**, 1438.
5. A. E. Hooper, S. R. Kennedy, C. D. Jones and J. W. Steed, *Chem. Commun.*, 2016, **52**, 198.
6. G. Smith, K. E. Baldry, K. A. Byriel and C. H. L. Kennard, *Aust. J. Chem.*, 1997, **50**, 727.
7. D. Maddileti and A. Nangia, *CrystEngComm*, 2015, **17**, 5252.
8. R. C. Bott, G. Smith, U. D. Wermuth and N. C. Dwyer, *Aust. J. Chem.*, 2000, **53**, 767.
9. D. M. Wood, B. W. Greenland, A. L. Acton, F. Rodríguez-Llansola, C. A. Murray, C. J. Cardin, J. F. Miravet, B. Escuder, I. W. Hamley and W. Hayes, *Chem Eur. J.*, 2012, **18**, 2692.
10. K. M. Anderson, A. E. Goeta and J. W. Steed, *Cryst. Growth. Des.*, 2008, **8**, 2517.
11. T. Steiner, *Acta Crystallogr., Sect. B*, 2000, **56**, 673.
12. J. W. Steed, *CrystEngComm*, 2003, **5**, 169.
13. K. M. Steed and J. W. Steed, *Chem. Rev.*, 2015, **115**, 2895.
14. N. J. Babu and A. Nangia, *Cryst. Growth Des.*, 2006, **6**, 1995.
15. B. P. van Eijck and J. Kroon, *Acta Crystallogr., Sect. B*, 2000, **56**, 535
16. R. Evans, Z. Deng, A. K. Rogerson, A. S. McLachlan, J. J. Richards, M. Nilsson and G. A. Morris, *Angew. Chem., Int. Ed.*, 2013, **52**, 3199.
17. C. A. Kingsbury, *Faculty Publications -- Chemistry Department. Paper 81.* http://digitalcommons.unl.edu/chemfacpub/81, 2015.
18. T. W. Panunto, Z. Urbanczyk-Lipkowska, R. Johnson and M. C. Etter, *J. Am. Chem. Soc.*, 1987, **109**, 7786.
19. A. Spek, *Acta Crystallogr. Sect. D*, 2009, **65**, 148.

Graphical Abstract

Hydrogen bond acceptor guests trigger solution and solid state cyclamer assembly in 5-ureaidsalicylic acid with up to 12 crystallographically independent molecules in the structure.